DETAILED ACTION

1. Applicant's amendment and remarks, filed 2/5/08, are acknowledged.

Claims 6 has been cancelled.
Claims 1-2 and 4 have been amended.
Claims 1-5 are pending and are under examination.

2. The rejection of the claims under 35 U.S.C. 102 as being anticipated by the '936 patent is withdrawn. The '936 patent does not teach a CD4+CD25+ suppressor T cell.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-5 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Hall et al. (of record).

As set forth previously, Hall et al. teach CD4+ suppressor T cells capable of inhibiting restoration of transplant rejection (i.e. decreasing transplant rejection) (see in particular page 154, Summary, lines 7-8). Additionally, Hall et al. teach CD4+ suppressor T cells to be CD45R (see in particular page 152, 2nd paragraph, line 1) and that $CD45R^+$ cells to be naïve cells (i.e. naïve CD4+ T cells) (see in particular page 152, 2nd paragraph, lines 14-15). However, Hall et al. do not teach the same process of making the claimed suppressor T cells. As regards to applicant's reliance upon product-by-process limitations within the claimed methods; it is noted that the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113. The claimed compound is the same compound as taught by Hall et al., irrespective of how it is made.

Applicant's arguments, filed 2/5/08, have been fully considered, but they are not persuasive.

Applicant argues that the cells taught by Hall et al. require CD8+ cells to mediate their suppressive effect, while the instant cells exhibit suppressive activity independent of CD8+ cells.

As an initial matter, the instant claims are not limited to suppressor T cells that mediate suppression independent of CD8

cells. Additionally, Applicant has not provided any evidence that the cells of the instant claims mediate suppression independent of CD8+ cells. The examples cited by Applicant (Figs. 2A-4B) do not address the suppressive ability of CD4+ T cells in the absence of CD8+ cells. In fact, CD8+ T cells (i.e. CTL) are present in these in vitro assays. Furthermore, Hall et al. demonstrate that suppressor CD4+CD25+ T cells delay graft rejection in the complete absence of CD8+ cells (compare line 1 and line 2 of table V, and see pages 149-150). Therefore, the cells of Hall et al. do mediate some degree of suppression in the absence of CD8 cells. The statement of Hall et al. cited by Applicant (i.e. that a CD8+ cell was critical for transfer of suppression by the suppressor cells) does not change the fact that the data in Table V demonstrate some degree of suppression of the CD4 cells in the complete absence of CD8 cells.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-5 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Groux et al., 1997, in view of Seder et al., 1998.

As set forth previously , Groux et al. teach a population of regulatory T cells (i.e. suppressor T cells) made by incubating a CD4+ enriched population of PBMC with irradiated allogenic monocytes (i.e. a donor population of mononuclear cells depleted of T cells, see page 739 in particular). Groux et al. also teach that the suppressive activity of the cells is mediated by their production of TGF-β (see page 70 in particular).

Groux et al. do not teach incubating the CD4+ T cells with TGF-β.

Seder et al. teach that incubating CD4+ T cells with TGF-β enhances the production of TGF-β by the T cells.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add TGF-β, as taught by Seder et al. to the cultures of regulatory T cells taught by Groux et al. The ordinary artisan at the time the invention was made would have been motivated to do so in order to enhance TGF-β production by the regulatory T cells, since Groux et al. teach that the suppressive activity of the regulatory T cells is mediated by their production of TGF-β, and Seder et al. teach that culture with TGF-β enhances TGF-β production by T cells. Furthermore, claim 5 is included since PBMC enriched for CD4+ cells are

enriched for naïve CD4+ T cells compared to the starting population of PBMC. Claim 3 is included since the patentability of a product does not depend on its method of production, and Groux et al. and Seder et al. make obvious the suppressor T cells of the instant claims.

Applicant's arguments, filed 2/5/08, have been fully considered, but they are not persuasive.

Applicant argues that the Tr1 cells taught by Seder et al. or Groux et al. are not the same as the CD4+CD25+ regulatory cells.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant further argues that neither Groux et al. nor Seder et al. teach combing the starting cells with donor irradiated T-cell depleted mononuclear cells.

Groux et al. teach regulatory T cells generated by contacting CD4+ T cells with allogeneic monocytes (i.e. donor T-cell depleted mononuclear cells).

Applicant further argues that Groux et al. teach away from the claimed invention, since they demonstrate that anti-TGF-β antibodies augments proliferation of regulatory T cells. Thus, Applicant concludes there would be no motivation to add TGF-β in a method of generating regulatory T cells, since it would inhibit their in vitro expansion.

Groux et al. teach that anti-IL-10 or anti-TGF-β antibodies, can in some circumstances (i.e. after restimulation of Tr1 cells with anti-CD3 or OVA peptide) enhance proliferation of regulatory T cells. However, Groux et al. also teach that anti-TGF-β antibodies do not effect the proliferation of regulatory T cells generated by stimulation allogeneic monocytes (see Fig. 2b, JDV23 TR1 cells). Thus, Groux et al. do not teach away from adding TGF-β to Tr1 cells made by stimulation with allogeneic monocytes (i.e. the instantly claimed invention). Furthermore, Seder et al. teach that adding TGF-β to cultures of regulatory T cells enhances TGF-β production, and Groux et al.

teach that TGF-β production by regulatory T cells mediates suppression. Therefore, the ordinary artisan would be motivated to add TGF-β in order to enhance the suppressive capabilities alloantigen specific regulatory T cells of Groux et al. Furthermore, the ordinary artisan would have a reasonable expectation of success, since Groux et al. teach that TGF-β does not inhibit the proliferation of regulatory T cells stimulated with allogeneic monocytes.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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